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## **Higher sleep spindle activity is associated with fewer false memories in adolescent girls**

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## **Abstract**

### **Background**

Sleep facilitates the extraction of semantic regularities amongst newly encoded memories, which may also lead to increased false memories. We investigated sleep stage proportions and sleep spindles in the recollection of adolescents' false memories, and their potential sex-specific differences.

### **Methods**

196 adolescents (mean age 16.9 y; SD=0.1, 61 % girls) underwent the Deese, Roediger & McDermott (DRM) false memory procedure and overnight polysomnography, with free recall the following morning. Sleep was scored manually into stages 1, 2, 3 and REM. Stage 2 sleep spindle frequency, density, and peak amplitude were used as measures of spindle activity for slow (10–13 Hz) and fast (13–16 Hz) ranges.

### **Results**

In girls, a lower number of critical lures was associated with higher spindle frequency ( $p \leq 0.01$ ), density ( $p \leq 0.01$ ), and amplitude ( $p = 0.03$ ). Additionally, girls' longer sleep duration was associated with more intrusion words ( $p = 0.03$ ), but not with critical lures. These associations survived adjustment for age, pubertal status, and intelligence. No significant results emerged in boys.

### **Conclusions**

In adolescent girls, higher spindle activity was associated with fewer critical lures being falsely recalled in the DRM paradigm. Unlike studies using adult participants, we did not observe any association between slow-wave sleep and false memory recollection.

**Keywords:** spindle activity, electroencephalography, teenager, sexual dimorphism, remembering, forgetting

## 1. Introduction

Memory consolidation is strongly associated with sleep (Diekelmann & Born, 2010). During sleep, the brain reorganizes newly encoded material, and through selection processes it aids in remembering things that, for example, have emotional content, that might have future relevance, or require further processing (Diekelmann, Wilhelm, & Born, 2009). Similarly, sleep supports forgetting unnecessary information (Saletin, Goldstein, & Walker, 2011). The process of reorganizing and consolidating memories is one of the central cognitive functions of sleep (Landmann et al., 2014).

The role of sleep in memory consolidation is not restricted to the reorganization of memories that were directly encoded during wake. Instead, growing evidence demonstrates that sleep also facilitates semantic processing (Landmann et al. 2014). The extraction of semantic regularities amongst the newly encoded memories can also be approached as the extraction of semantic “gist” (Cann, McRae, & Katz, 2011). The best known paradigm for studying the extraction of gist is the Deese-Roediger-McDermott (DRM) false memory paradigm. In this task participants encode lists of words (*studied words*, e.g., nurse, hospital, medicine...) that are all related to a common semantic theme within the list. Critically, each list is associated with a *critical lure*, a word that participants never study but which is closely related to the semantic theme of the list (e.g., doctor) (see Figure 1 for illustration of the paradigm). When participants later are asked to recall the studied words and produce *correctly recalled words*, they typically falsely recall the critical lure. Additionally, participants in free recall tasks often return several other false words, or *intrusions*, which were neither present in the study lists nor related to the meaning of the lists.

Conditions that lead to increased false memory for critical lures are ones that likely facilitate semantic processing of newly encoded memories. Sleep has been shown to be one such

condition. In studies with adult participants, sleep (relative to wake) after exposure to the study lists in the DRM paradigm has been shown to increase false recall of critical lures both when tested in free recall (Payne et al., 2009) and in recognition memory tasks (Fenn, Gallo, Margoliash, Roediger, & Nusbaum, 2009; Shaw & Monaghan, 2017). Recent studies have begun to shed light on the aspects of sleep architecture that are involved with the generation of false memories. For example, higher amount of slow wave sleep (SWS) in relation to sleep duration was associated with fewer false memories, but only among those with poorer true memory recall (Pardilla-Delgado & Payne, 2017; Payne et al., 2009).

Previous studies have suggested that sleep deprivation enhances the formation of false memories (Diekelmann, Landolt, Lahl, Born, & Wagner, 2008). This may be partially due to oversimplifying a schema when cognitive resources are reduced. While false memories may represent an actual error in memory, they may additionally be seen as an adaptive mechanism of memory consolidation, which is helpful in everyday life settings. Thus, the findings from false memory studies may represent aspects of both beneficial and adverse adaptation mechanisms, as suggested by Diekelmann and others (Berndt, Diekelmann, Alexander, Pustal, & Kirschbaum, 2014; Diekelmann, Born, & Wagner, 2010).

Another aspect of sleep which has recently been associated with false memory recollection is sleep spindle activity. Sleep spindles are bursts of neural activity as measured by thalamo-cortical oscillations in the 10-16 Hz range, typically during stage 2 sleep (De Gennaro & Ferrara, 2003), but also in SWS. While sleep spindles occur both in stage 2 and SWS, their density is higher in stage 2 relative to SWS, especially among younger individuals (e.g. spindle density 1.88 per minute in stage 2 sleep vs. 1.45 per minute in SWS), and are considered the hallmark of stage 2 sleep (Baker et al., 2016)(Purcell et al., 2017). Spindles are known to be associated with cognitive

processing, with several studies reporting an increase in spindle activity when processing newly acquired information during sleep (Gais, Molle, Helms, & Born, 2002; Hoedlmoser et al., 2014). Spindle activity in stage 2 and in SWS seems to serve other functions besides indicating memory consolidation processes: several studies have suggested that spindles aid in maintaining sleep and suppressing external disturbances (Astori, Wimmer, & Luthi, 2013; Luthi, 2014). Based on the literature, there seems to be two fundamentally distinct human spindle classes; (1) fast spindles, which are thought to be related to direct memory consolidation and (2) slow spindles, which appear after the fast spindle, approximately 500ms later (Molle, Bergmann, Marshall, & Born, 2011).

A recent study using a daytime-nap setting and the DRM paradigm found that the degree to which spindles were lateralised to the right hemisphere, but not the raw number of spindles, predicted the number of false memories generated after sleep (Shaw & Monaghan, 2017). This led the authors to propose that false memories are generated in the right hemisphere, and that sleep spindles facilitate this process by consolidating the studied word lists in semantic memory. This view is consistent with work showing that sleep spindles facilitate integration of newly learned words with existing knowledge (Tamminen, Lambon Ralph, & Lewis, 2013; Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010).

The weight of the current evidence therefore suggests that sleep facilitates generation of false memories, and that this process is possibly modulated by sleep spindle activity and SWS. However, all of the studies discussed above have been carried out on adult participants. Whether the same mechanisms apply to other age groups is a poorly understood issue. This is particularly true of adolescence: while there is a growing literature on sleep and memory in young children (Wilhelm, Prehn-Kristensen, & Born, 2012) and in elderly populations (Scullin & Bliwise, 2015), adolescence remains relatively unexplored. Yet adolescence is a time of profound change in many

domains, including sleep, which may mean that what we know about the impact of sleep on memory in adults and in young children may not apply to adolescents. Some of the most salient sleep-related changes in adolescence pertain to changes in the distribution of sleep stages. As children enter adolescence, they experience a dramatic decline in SWS, accompanied by an increase in stage 2 sleep and sigma EEG activity which is related to sleep spindles (Tarokh & Carskadon, 2010). These changes mean that adolescence can be seen as a period of transition from child-like sleep (typically heavier on SWS) towards adult-like sleep (Baker et al., 2016) (lighter on SWS, heavier on spindle density and frequency) (Purcell et al., 2017). As these changes affect the two features of sleep which in the adult literature have been implicated in false memory recollection, it is important to investigate the impact of sleep on adolescent memory.

Despite spindles being more prevalent in stage 2 sleep than other stages, SWS spindles and their interactions with other oscillations are beginning to gain attention as a potential pathway to memory consolidation (Antony et al., 2018) (Cairney, Guttesen, El Marj, & Staresina, 2018). Thus, there seems to be growing evidence suggesting that spindle-oscillation-coupling is an important mechanism for certain types of memory consolidation, though no studies relating to false memories in SWS spindles have yet been published. The focus in the current study will be on stage 2 spindles.

As a first step to understand how sleep is associated with false memory recollection in adolescence, we tested a large sample of healthy adolescents consisting of both girls and boys. Participants studied DRM lists in the evening, followed by a polysomnographically monitored night of sleep. Memory for studied words and production of critical lures in free recall was tested in the morning. Given that the only existing studies looking at sleep architecture and false memory formation concern adult populations, our hypotheses were guided by this literature. We predicted that if sleep operates in a similar manner in adults and adolescents, stage 2 sleep spindles would

likely facilitate overnight false memory recollection and that SWS might be negatively correlated with the number of false memories.

Based on studies suggesting sex-specific differences in the relationship between sleep and cognitive performance (Bodizs, Gombos, Ujma, & Kovacs, 2014; Genzel et al., 2012; Santhi et al., 2016), we also investigated the possible role of sexual dimorphism, which may be emphasized at this point of development when pubertal maturity differences are present also on a neural level (Campbell, Grimm, de Bie, & Feinberg, 2012). The differences between adolescent girls and boys in this relation have been a topic of interest as it is evident that in girls pubertal development may be reflected in sleep structures at an early age (Campbell et al., 2012; Philbrook, Hinnant, Elmore-Staton, Buckhalt, & El-Sheikh, 2017; Santhi et al., 2016), and thus differences in sleep dependent cognitive performance may vary according to sex. Baseline differences in either sleep or cognition may explain some of the variation, but, also the sexual dimorphism in the associations between sleep and cognition have been reported (Genzel et al., 2012), also in a previous follow-up of this study population (Kuula et al., 2015).

## **2. Materials and Methods**

### **2.1 Participants**

The participants came from an urban community-based cohort composed of 1049 healthy singletons born between March and November 1998 in Helsinki, Finland (Strandberg, Jarvenpaa, Vanhanen, & McKeigue, 2001). Detailed descriptions of the cohort and participation flow are found elsewhere (Kuula et al., 2017; Pesonen et al., 2014). Due to original research interests, the flow of participation was weighted on those whose mothers reported higher liquorice consumption during pregnancy. In the current study, those adolescents who had participated in the previous follow-up, and who lived within a 30 kilometre radius of Helsinki and had given consent for further contact,

were recruited by phone. The participants were recruited in the order of their birthday, resulting in a narrow age range in the current sample.

Participants underwent overnight polysomnography (PSG) in late adolescence (mean age 16.9 y, SD=0.1, range 16.6-17.2) in their own home, and received a monetary compensation (50€) for their effort. All in all, 196 adolescents participated (61 % girls) and produced data for the false memory test. Out of the 196 adolescents, 185 produced EEG data of sufficient quality: 4 boys and 7 girls had to be excluded from the sleep spindle analyses due to poor impedance levels or other measurement problems.

The Ethics Committee of the Children's Hospital in Helsinki University Central Hospital approved the study protocol (177/13/03/03/2014). Informed written consent was obtained from the participants. All parts of the study were conducted in accordance with the Declaration of Helsinki.

## **2.2 PSG protocol and spindle detection**

The sleep measurements were arranged according to the participants' schedules, and were done over the school year from January to December, excluding July due to summer holidays. 90 % of all PSG recordings were completed on school nights. All recordings were done using SOMNOscreen plus (SOMNOmedics GmbH, Germany). A trained research nurse attached gold cup electrodes at 6 EEG locations (frontal (F) hemispheres: F3, F4; central (C) hemispheres: C3, C4; occipital (O) hemispheres: O1, O2) and two for the mastoids (A1, A2) accordingly. In addition to hemisphere-specific measures, we calculated overall frontal and central measures as means from both hemispheres. The electro-oculogram (EOG) and the electromyogram (EMG) were measured by using disposable adhesive electrodes (Ambu Neuroline 715, Ambu A/S, Denmark), two locations for EOG and three locations for EMG. In addition, an online reference Cz and a ground electrode in the



middle of forehead were used. The sampling rate was 256 Hz (the hardware filters for SOMNOscreen plus are 0.2-35Hz).

All signals were digitally offline filtered with pass band of 0.5-35Hz (Hamming windowed sinc zero-phase FIR filter, cut-off (-6dB) 0.25Hz and 39.3Hz respectively) and re-referenced to the average signal of A1 and A2 electrodes. PSG data were scored manually using the DOMINO program (v2.7; SOMNOmedics GmbH, Germany) in 30-sec epochs into Stage 1, Stage 2, SWS and REM according to AASM guidelines (The AASM Manual for the Scoring of Sleep and Associated Events (Berry et al., 2012)). Percentages of each stage were calculated based on total sleep time.

Spindles were computationally extracted with the method described by Ferrarelli (Ferrarelli et al., 2010), which has been widely used in other studies relating to sleep and memory (Tamminen et al., 2013; Tamminen et al., 2010). The manually scored PSG signals were converted to EDF format in DOMINO software and then pre-processed for spindle detection by using functions of EEGLab 13.5.4b (Delorme & Makeig, 2004) running on Matlab R2015a (The Mathworks Inc., USA).

We extracted spindles from EEG (Stage 2 sleep), with electrode-scalp impedance equal or lower than 10k $\Omega$  during the corresponding 30-second epoch; only Stage 2 epochs with sufficiently low impedance values were included in the spindle analyses. The spindle analysis was conducted in two different frequency bands (slow: 10-13Hz, and fast: 13-16Hz) in order to differentiate between the slow and fast spindles, which are likely to serve different functions in sleep (Wallant, Maquet, & Phillips, 2016). Before applying the spindle thresholding method, the pre-processed EEG data were further filtered using the above-mentioned frequency bands separately. The threshold values for finding spindle peak amplitude in each channel were defined by the mean of the channel amplitude ( $\mu$ V) multiplied by 2 (lower) and 8 (higher) including all valid epochs (Stage 2 and impedance  $\leq$  10k $\Omega$ ).

Thus, we used channel-wise threshold definitions, taking into account that signals may vary across the channels. Furthermore, the duration for a valid spindle was set to 250-1000ms in both directions from the peak maximum. Outside this time window, signal amplitude was required to stay under the lower threshold at least for 78.1ms which is approximately the duration of one sine period at 13Hz. This was done in order to prevent false alarms in spindle detection. We have recently published a detailed description of the spindle detection (Merikanto et al., 2017). Spindle frequency, peak amplitude ( $\mu\text{V}$ ), and density (number of spindles per minute) were used as measures of individual spindles and general spindle activity.

## **2.3 Experimental Design and Statistical Analysis**

### **2.3.1 False memory protocol**

*[Figure 1 around here]*

*[Figure 1 - Schematic illustration of the Deese, Roediger & McDermott (DRM) protocol. The critical lure overlaps semantically with studied words.]*

We used the standard Deese, Roediger & McDermott (DRM) procedure illustrated in Figure 1 to induce false memories. The procedure was translated into Finnish. All participants were presented with the same recording of eight DRM lists of 15 words (altogether 120 words studied in random order) in the evening before the PSG measurement. Each of the eight lists corresponded to a

common semantic theme (window, sleep, smell, doctor, sweet, smoke, soft, mountain). These eight lists were selected on the basis of being the most likely ones to result in false recall, as reported previously (Stadler, Roediger, & McDermott, 1999).

Subjects listened to the words in their own bedrooms where the words were presented via earphones while the research nurse was present. They were instructed to try to memorize the words as they would be tested the following morning, but they were not told that the words are related. The critical lures were never presented during the learning phase. The lists were recorded electronically in a female voice and presented once sequentially through earphones in the evening before going to bed. In the morning, after a full night's sleep and usual morning routines, the research nurse unwired the participant, and asked the participant to recall as many words as possible, with no formal time limit for free recall. The research nurse made notes of all the words from free recall, and the words that the participant produced were later categorized into Correctly recalled studied words, Critical lures, and, Intrusions.

### **2.3.2 Statistics**

All statistical analyses were done using IBM SPSS Statistics version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Significance was set at  $p < 0.05$ . Baseline differences between groups were analysed using T-tests and chi square ( $\chi^2$ ) tests.

After preliminary data inspection, we excluded two outlier participants from certain analyses due to scores differing several standard deviations (SDs) from mean (one male scored 3.7 SDs above mean of correctly recalled words, and another scored 4.8 SDs above mean of intrusions). In order to investigate whether their exclusion caused any bias, we re-ran the analyses with these participants included, and found no significant difference in the results (data not shown).

The number of correctly recalled studied words, critical lures, and intrusions (i.e. falsely recalled words that were neither studied nor critical lures) were used in linear regression analyses as continuous outcome variables. Sleep stages and sleep spindle amplitude, density, and frequency were used as predictor variables. Based on this, we set out to examine the associations between sleep variables and DRM test performance using two models. As a crude Model 1, we only controlled for age. Model 2 included further covariates for those confounding variables that correlated significantly with the outcome variables (see *Potential confounders* for details).

In order to study whether baseline differences between girls and boys carried an additional weight towards predicting false memory recollection, we completed interaction analyses for 'spindle\*sex' interaction effects regarding the false memory performance.

As a more detailed approach relating to memory accuracy, we additionally calculated the proportional amount (%) of critical lures in relation to all correctly remembered words by dividing the number of critical lures by total number of correctly recalled studied words. This ratio measure reflects the semantic processing of the studied word lists. Due to a nonparametric distribution, we divided this measure into quartiles (Q1-Q4 with Q1 representing smallest ratio and Q4 largest). This was done separately for girls and boys, as the data inspection showed significant sex differences. We then analysed the differences in sleep stages and spindle variables between quartiles (Q1-Q4) using ANCOVAs.

In order to control for Type I error caused by multiple testing in the spindle analyses, we used a false detection rate procedure (FDR) (Benjamini & Hochberg, 1995). When using this procedure, an additional critical value is calculated for each hypothesis test, based on the number of tests and what is considered an acceptable Type I error rate. The critical values are calculated using a formula that places the most stringent critical values against the most significant results. We

set the false discovery rate across 18 tests (3 spindle variables x 3 DRM tests x 2 spindle locations) at 0.05, which can be considered a conservative limit. Based on extremely correlated variables, neither the frequency band range nor the test for false memory ratio were treated as separate dimensions in the FDR procedure ( $p \leq 0.0001$  for the correlation between slow and fast spindle variables and  $p \leq 0.0001$  for correlation between false memory ratio and critical lures).

## **2.4 Covariates and potential confounders**

Age at the time of the study was calculated based on hospital birth registers. Information on sex was also derived from hospital records. As this is a well-characterized birth cohort, we also investigated the relationship between the DRM task performance and potential confounders, such as body-mass index ( $\text{kg}/\text{m}^2$ , BMI), intelligence quotient (IQ), pubertal development (Petersen, 1988), menstrual cycle phase (Genzel et al., 2012), parental education as a marker of socio-economic status (SES), Morningness-Eveningness preference (Hatonen, Forsblom, Kieseppa, Lonnqvist, & Partonen, 2008), and, due to original research interests, maternal liquorice consumption during pregnancy (Raikkonen et al., 2017; Strandberg et al., 2001). BMI was calculated from height and weight measurements, which were carried out by the research nurse who completed the PSG measurement protocol. IQ was calculated based on four subtests from the Wechsler Adult Intelligence Scale III (Wechsler, 1997), pubertal development was measured using the validated Pubertal Development Scale (PDS) (Petersen, 1988), menstrual cycle phase was calculated from self-reports, and, SES was defined as the highest self-reported education level of either parent at the previous follow up (2011-2012). SES was classified as (1) secondary or lower, (2) vocational degree, or (3) university degree. Morningness-Eveningness was self-reported using a short version of Horne-Östberg's questionnaire (Hatonen et al., 2008; Horne & Ostberg, 1976). Maternal liquorice

consumption was self-reported and classified as low consumption (<250mg/week) or moderate to high consumption ( $\geq$ 250mg/week)(Raikkonen et al., 2009).

As it is possible that there is a difference in performance across weekends and weekdays, we also investigated mean level variation between weekday/weekend DRM test performances. Similarly, we investigated the potential role of sleep inertia by calculating the correlation between DRM test performance measures and the amount of time between wake-up time and DRM test start time.

### **3. Results**

#### *3.1 Sample characteristics*

Table 1 presents the descriptive characteristics, DRM task performance as well as the PSG and spindle variables of the participants separately for girls and boys. Out of these characteristic and sleep variables, girls and boys differed from each other in some aspects: girls had a more advanced pubertal status, smaller Stage 1 percentages, larger Stage 2 percentage, and had significantly stronger spindle activity in the central region, fast range, whereas boys had higher spindle frequency as derived from the central region, slow range and the frontal region, fast range.

Regarding the DRM memory task, girls recalled significantly more studied words than boys, and produced significantly more false memories in the form of critical lures than boys. However, the false memory ratio, which corrects for bias in general response productiveness, showed that in fact boys were significantly more likely to produce false memories than girls. Given that girls appeared to have a more liberal criterion in entering responses, and given the significant difference in false memory ratio between boys and girls, the subsequent analyses regarding false

memory and aspects of sleep architecture were carried out separately for boys and girls to take into account potential sex differences. Furthermore, interaction analyses suggested significant 'spindle\*sex' interaction effects for false memory performance ( $p \leq 0.001$ ) between male and female participants, so all further analyses were done separately for girls and boys.

*[Table 1 around here]*

***[Table 1 – Characteristics of the participants.]***

### *3.2 Potential confounders*

The examined potential baseline confounders (BMI, IQ, pubertal development, menstrual cycle phase, SES, Morningness/eveningness, maternal liquorice consumption, ) were not significantly associated with any of the DRM task outcomes (all  $p$ -values  $> 0.20$ ) except for overall intelligence and pubertal development, which correlated with the number of correctly recalled studied words ( $r=0.45$ ,  $p<0.0001$  and  $r=0.35$ ,  $p<0.0001$ , respectively), critical lures ( $r=0.27$ ,  $p<0.0001$  and  $r=0.19$ ,  $p<0.01$ , respectively), and intrusions ( $r=0.17$ ,  $p=0.02$  and  $r=0.15$ ,  $p=0.04$ , respectively). These were added as covariates in Model 2. Pubertal development (PDS) had five significant associations with the sleep spindle measures (Central fast frequency  $r=0.22$ ,  $p=0.006$ ; Frontal fast frequency  $r=-0.21$ ,  $p=0.007$ ; Frontal slow frequency  $r=0.24$ ,  $p=0.002$ ; Central fast density  $r=0.25$ ,  $p=0.002$ ; Central fast amplitude  $r=0.31$ ,  $p=0.0001$ ), and IQ score had three significant correlations (Frontal fast frequency  $r=-0.17$ ,  $p=0.024$ ; Central slow density  $r=-0.16$ ,  $p=0.042$ ; Central fast amplitude  $r=0.23$ ,  $p=0.003$ ). Detailed associations between IQ scores and sleep measures in this sample have been reported in Pesonen et al. 2018 (R1 submitted). None of the sleep stage measures were correlated with pubertal development or IQ.

Regarding other measures, we found no mean level significant differences when analysing the differences in DRM recollection over weekdays and weekends ( $p$ -values  $> 0.49$  for all DRM test measures). Also, none of the correlations between DRM test outcome measures and time



between wake-up time and DRM test start time were significant (all  $p$ -values  $> 0.38$ ), suggesting little influence from sleep inertia. As a further measure of controlling for weekend-weekday variation in performance we re-ran the analyses using only those participants with weekday registrations and found no differences in the significant results (data not shown).

### *3.3 Sleep stage and spindle analysis*

Table 2 presents the associations between DRM task memory performance and proportion of total time spent in each sleep stage for girls and boys. In girls, longer sleep duration was associated with a higher amount of intrusion words ( $p \leq 0.03$ ); no other associations relating to sleep amount were significant in girls ( $p > 0.05$ ) or boys ( $p > 0.05$ ). Table 3 presents unstandardized coefficients (B) from sleep spindle and continuous DRM variables in the regression analyses for girls (controlled for age; Model 1), and Table 4 for boys (controlled for age; Model 1).  $P$ -values for Model 2 (controlled for age, age-standardized intelligence scores, and pubertal development) are presented in Table 3 and Table 4. After controlling for multiple testing using the FDR procedure, the significant associations between DRM recollection and spindle density and frequency remain (see Table 3 for details). In girls, higher slow range spindle amplitude derived from the frontal region was associated with returning fewer critical lures. However, this association did not survive the FDR procedure correcting for multiple testing.

In models 1 and 2, girls' higher spindle density in the slow range was associated with a smaller number of critical lures (all  $p$ -values  $< 0.01$ ). In Model 2, slow range spindle density derived from the central region was associated with a greater number of correctly recalled, studied words ( $p = 0.039$ ) in girls. Additionally, girls' higher spindle frequency derived from both the central and frontal region in the slow range was associated with returning fewer critical lures. However, we also

found that higher frontal region fast spindle frequency was associated with more critical lure production.

While these results regarding overall DRM performance reveal some aspects of memory, it is likely that response style plays a part in the accuracy of false memory recollection. We calculated a ratio score in order to adjust for this potential confounder.

With false memory ratio quartile 1 (Q1) representing the most accurate performance (i.e. few false memories in relation to correctly recalled words) and quartile 4 (Q4) the least accurate (i.e. more false memories), the following differences were significant when investigating the associations of spindle activity in girls and controlling for age (Model 1): Central slow frequency [ $F(3,79)=2.83$ ,  $p=0.044$ ]; Central fast density [ $F(3,81)=3.33$ ,  $p=0.024$ ] and Central slow density [ $F(3,79)=6.84$ ,  $p=0.00037$ ]. This suggests that the most accurate memory was found in those with highest overnight spindle activity, although the associations were not fully linear. No differences were significant in boys in Model 1.

*[Table 2 around here]*

**[Table 2 – Associations between DRM test performance and sleep stages (Model 1: controlled for age; Model 2: controlled for age, pubertal development and IQ).]**

*[Table 3 around here]*

*[Table 3 – Associations between girls' false memory task performance and sleep spindles adjusted for age (Model 1); p-values presented for both Model 1 and Model 2 (controlled for age, pubertal development and estimated IQ).]*

*[Table 4 around here]*

*[Table 4 –Associations between boys' false memory task performance and sleep spindles adjusted for age (Model 1); p-values presented for both Model 1 and Model 2 (controlled for age, pubertal development and estimated IQ).]*

*[Figure 2 around here]*

*[Figure 2 - Differences in spindle density (Panel A), amplitude (Panel B) and frequency (Panel C) between false memory ratio quartiles 1-4. Significance marked \*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ .]*

Figure 2 illustrates the significant differences between girls' false memory ratio quartiles and spindle density (Panel A), spindle frequency (Panel B), and spindle amplitude (Panel C), representing adjustments according to Model 2. In Model 2 the following differences were significant when investigating the associations of spindle activity and the false memory ratio in girls (when controlling for age, pubertal development and intelligence): Frontal slow frequency [ $F(3,93)=2.73$ ,  $p=0.048$ ]; Central slow frequency [ $F(3,75)=3.90$ ,  $p=0.012$ ]; Central fast density [ $F(3,77)=3.57$ ,  $p=0.018$ ] and Central slow density [ $F(3,75)=7.67$ ,  $p=0.000155$ ]. Thus, the associations between accurate memory and higher spindle activity were not attenuated by intelligence or pubertal development in girls. No differences were significant in boys in Model 2.

#### **4. Discussion**

In this study, we investigated for the first time in a large sample of adolescents how whole night stage 2 spindle activity and sleep architecture were associated with free recall memory performance and false memory recollection in the DRM paradigm. We found an association between higher overnight stage 2 spindle activity and more accurate memory recollection, specifically in adolescent girls. The most marked associations were those between false memory ratio measuring accurate

memory recall and sleep spindle density suggesting that the overall pattern of spindle activity is associated with more accurate memory. While there was no clear pattern in the central vs. frontal location of the spindles, most of these associations were found in the slow range of spindle activity. The cognitive differences between slow and fast spindles are poorly understood, but our data are in line with the view that slow spindles are associated with more demanding memory tasks (Schmidt et al., 2006). Notably, these associations were found while controlling for intelligence. This is critical since some studies suggest that intelligence is positively correlated with baseline spindle activity (Fogel & Smith, 2011). Our data, however, suggest that sleep spindle activity is associated with false memory recollection over and above its association with intelligence.

In our study, higher stage 2 spindle activity in the slow range was consistently associated with fewer false memories. This is inconsistent with the theory proposed by Shaw and Monaghan (Shaw & Monaghan, 2017) whereby spindle activity facilitates the consolidation of studied DRM lists into semantic memory. However, their study involved a sample of adult participants, and did not examine overnight spindles, suggesting a potential difference between the impact of a full night of spindle activity and a brief daytime nap, and a difference between adult and adolescent sleep. Their findings were also restricted to lateralised sleep spindles, while our study focused on both hemispheres. Also, in their protocol, subjects were asked to recognise rather than freely recall the words, which may tap onto a different response mechanism (Chatburn, Lushington, & Kohler, 2014).

A recent review concluded that different learning paradigms benefit from either fast or slow range spindles, and that complexity as well as task domain play a part (Ulrich, 2016). Previous studies in memory consolidation have suggested that sleep spindles, especially (but not exclusively) in the fast range are predominantly associated with better performance in experiments

relating to memory, particularly in declarative tasks (Cairney et al., 2018; Schabus et al., 2004; Tamminen et al., 2010). However, this is not always the case: one study with young adult male participants reported a negative association between overnight retention and *trait-like aspects* of fast sleep spindle density and positively with slow spindle density on a global level (Lustenberger, Wehrle, Tushaus, Achermann, & Huber, 2015). Thus, it seems that trait-like aspects of spindle activity as well as task complexity may contribute to our slow-range specific findings. In addition, frontal slow spindles become more prominent with age; there is a sudden increase in frequency during puberty – this may be one contributor to our findings (De Gennaro & Ferrara, 2003).

It is noteworthy that we did find one association in line with the previous adult nap-study –finding: higher frontal region fast spindle frequency was associated with more critical lure production. While this finding was an individual result, it may imply a different mechanism associating to fast spindles, perhaps relating to the timing or temporal coupling to slow oscillations as suggested by previous literature from a SWS study (Molle et al., 2011). We have no explanation for the one separate, positive association, but we speculate that the positive association might be an indicator of the processing of newly acquired memories while slow spindle activity may play a role in more complicated, selective processing (Schmidt et al., 2006). However, this is merely speculative and based on our data no further evidence can be perceived.

Regarding sleep stages, the previously reported negative correlations between SWS and false memory in young adults (Pardilla-Delgado & Payne, 2017) and in older adults (Lo, Sim, & Chee, 2014) were not replicated in our study with adolescents, although a similar negative correlation was found with spindles. Given that SWS is more dominant in childhood than in adulthood, and that adolescents are in a stage of transitioning from childhood towards adulthood, this may reflect a developmental difference in the role SWS and sleep spindles play in memory

consolidation processes. More research into the role of sleep in memory and learning in adolescence is needed to confirm this hypothesis and to understand better possible developmental changes in sleep and memory during this period of transition.

It is likely that some features of sleep spindles are stable trait-like features (Levendowski et al., 2017), whereas some other features may be more dependent on external stimuli, or, for instance, pre-measurement activities (Yordanova, Kirov, Verleger, & Kolev, 2017). This may also partially explain the reported relationship between intelligence and spindle activity (Fogel & Smith, 2011). While spindle activity is thought to be a marker of neural plasticity, it is unknown whether the morphological parameters of individual spindles or overall overnight spindle activity is a more prominent marker of said plasticity. The only previous spindle study reporting false memory recollection using the DRM protocol focused on an experimental nap setting (Shaw & Monaghan, 2017), thus not being comparable to overnight spindle studies. Based on our results, it would seem that higher overnight spindle density and frequency, but not amplitude, is associated with a more accurate memory. The current study does not answer this question and it needs to be further investigated in experimental settings.

Our study focused only on stage 2 spindles. Spindles also occur during other stages, namely during SWS, although the spindle activity is significantly lower. While spindles are the hallmark feature of stage 2 sleep and seem to be a central in optimal memory function, future research should also investigate whether SWS oscillations contribute to memory consolidation as stage 2 and SWS spindles may serve different purposes. It is likely that spindles and other oscillations participate in memory consolidation processes in complementary roles: sleep spindles during stage 2 sleep and slow oscillations during SWS as well as the order of sleep stages during natural sleep is

hypothesized to be critical in preventing interference and enhancing consolidation (Wei, Krishnan, Komarov, & Bazhenov, 2018). This is a question for future studies.

As previous studies have underlined the differences between male and female subjects regarding both sleep and its associations with cognition (Campbell et al., 2012; Santhi et al., 2016; Sattari et al., 2017), we investigated how girls and boys differ during adolescence in this respect. While the role of spindles in relation to cognitive ability is under debate, it seems plausible that spindle activity shows some degree of sex-specific features (Bodizs et al., 2014; Ujma et al., 2014), and that these differences contribute to the findings in our study.

In the current study, we found evidence for the sexual dimorphism of the developing brain; greater spindle activity and better memory performance were significantly associated only in girls. Several studies have reported different associations in cognition and neural activity between girls and boys during adolescence (Lenroot & Giedd, 2010; Paus et al., 2010). It may also be noted that pubertal development and several sleep parameters differed between girls and boys to begin with, so it is possible that the underlying differences in neural maturation partially explain the different findings in this study. As girls' neural development is more mature at this age, similar findings may emerge in boys at a later age. Using a self-report for measuring physical attributes of pubertal development only enables controlling for secondary pubertal changes – this approach might not detect those neural alterations that are relevant for sleep EEG measures.

#### *4.1 Strengths and limitations*

Our study is the first to report associations between spindle activity and false memory recollection in adolescent girls and boys. As strengths, the sample size in this study is sufficient to be representative of neural activity in this developmental phase. The EEG measurements were done in the participants' own homes, which decreases any possible sleep laboratory effect, and thus further



increases the representativeness of our study's results. Additionally, due to our recruitment order, we were able to focus on a very narrow age range, thus eliminating the effect of age on our findings.

As a major limitation, our study setting did not include a wake-control group, and thus, it is impossible to determine any causal effects of sleep per se in the current study. However, studies comparing wake and sleep regarding false memory formation have been reported (Fenn et al., 2009; Payne et al., 2009), and even though these studies do not result in any definite conclusions regarding false memory formation, they suggest that sleep, compared to wake, produces different effects.

As a further limitation, our PSG measurement covered only one night, which may cause some effect on sleep architecture. We relied also here on an associational design, without any experimental manipulation for the memory performance, and thus any causality cannot be claimed. However, the reliance on a naturalistic setting also brings advantages by adding significant ecological validity to the study. Future research should determine the influence of stable, trait-like features in individual spindle activity on false memory formation. This would aid in pinpointing the causality of spindle-related encoding mechanisms: some spindle activity may result as a response to increased material encoding, while other aspects of spindle activity may depend more on trait-like underlying spindle-generating mechanisms. Future research should, thus, address the trait-like spindle activity of study participants by utilizing experimental settings or including several nights of testing and measurements. This would aid in determining the possible causality of the associations we found in the current study.

#### *4.2 Conclusions*

We found that in adolescent girls, higher stage 2 spindle activity was associated with fewer critical lures being falsely recalled in the DRM paradigm, and overall more accurate memory recall. These results were not attenuated when controlling for intelligence. Unlike studies using

adult participants, we did not observe any association between SWS and false memory recollection. Given that our sample size was larger than in most adult studies, this is not likely to be due to lack of statistical power. We suggest that developmental changes in sleep architecture from childhood to adolescence to adulthood may result in a changes in the memory-related cognitive functions served by SWS and sleep spindles. As our study is the first to investigate the role of sleep in false memory recollection in adolescence, and one of a very small number of studies looking at sleep and memory in this underrepresented age group, we call for further research to clarify how different aspects of sleep consolidate different types of memory in adolescent participants. In the meanwhile our data suggest that sleep spindles, not SWS, protect adolescent participants against false memories.

## **5. Disclosure Statement**

Declarations of interest: none

## **6. Acknowledgements**

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**7. Author contributions:** LK and AKP designed the study, and TM contributed significantly to developing methods. TM, LK and AKP contributed in the data collection. LK and AKP conducted data analysis. LK wrote the initial manuscript with JT, and AKP, TM, IM and KR revised the manuscript for important intellectual content.

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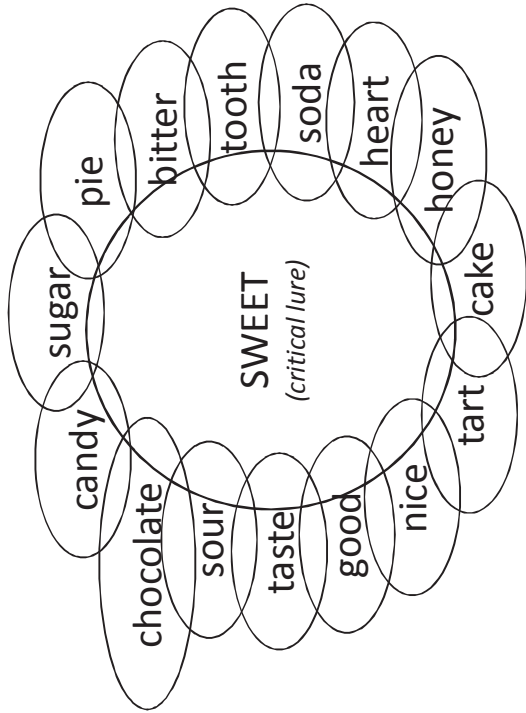
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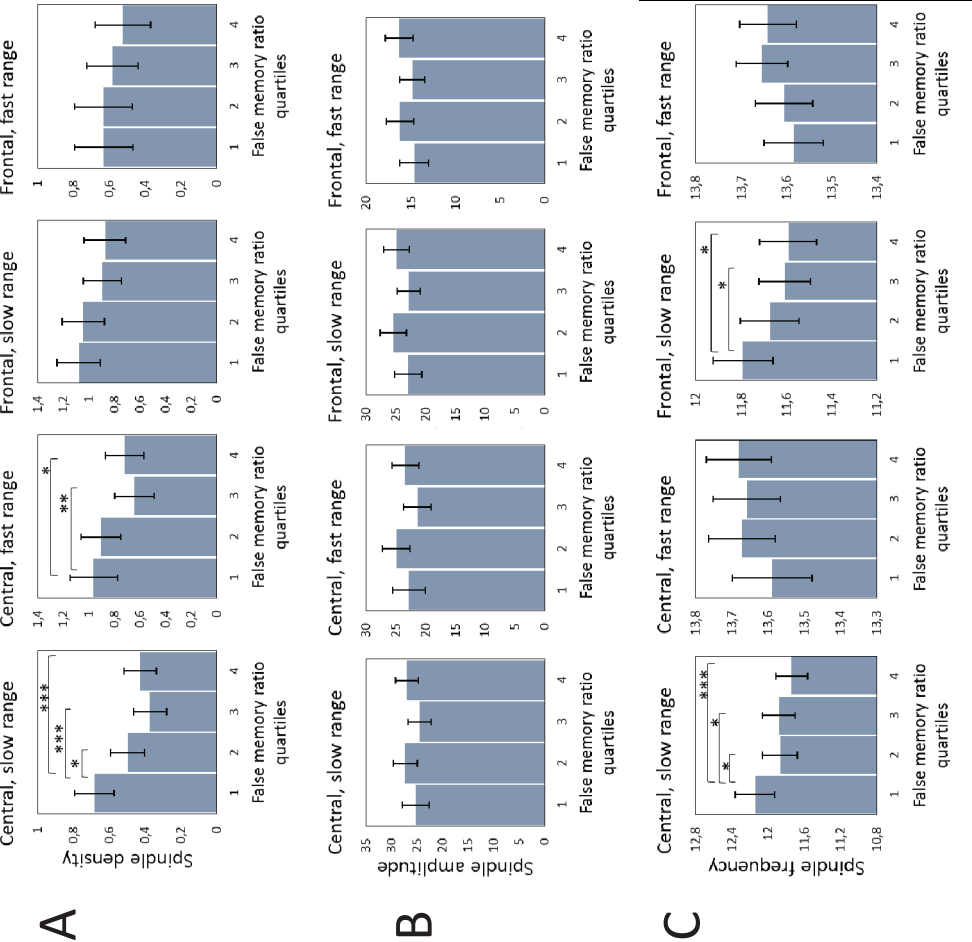
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**Figure 1** – Schematic illustration of the Deese, Roediger & McDermott (DRM) protocol. The critical lure overlaps semantically with studied words.



**Figure 2** – Differences in spindle density (Panel A), amplitude (Panel B) and frequency (Panel C) between false memory ratio quartiles 1-4 in girls (Model 2). Significance marked \*\*\*  $p<0.001$ ; \*\* $p<0.01$ ; \* $p<0.05$ .



**Table 3** – Associations between girls’ false memory task performance and sleep spindles adjusted for age (Model 1); p-values presented for both Model 1 and Model 2 (controlled for age, pubertal development and estimated IQ).

	Correctly recalled words			Critical lures			Intrusions		
	B	(95 % CI)	*p <sup>1</sup> /p <sup>2</sup>	B	(95 % CI)	*p <sup>1</sup> /p <sup>2</sup>	B	(95 % CI)	*p <sup>1</sup> /p <sup>2</sup>
<u>Amplitude (µV)</u>									
Central, slow	-0.04	(-0.17, 0.09)	0.55/0.14	-0.34	(-1.27, 0.59)	0.47/0.29	-0.08	(-0.37, 0.20)	0.56/0.40
Central, fast	0.03	(-0.10, 0.16)	0.66/0.94	-0.39	(-1.34, 0.56)	0.41/0.19	0.02	(-0.27, 0.31)	0.89/0.95
Frontal, slow	-0.14	(-0.25, -0.03)	0.02/0.01 <sup>†</sup>	-0.82	(-1.61, -0.03)	0.04/0.03	-0.26	(-0.49, -0.03)	0.03/0.04
Frontal, fast	-0.08	(-0.16, 0.00)	0.04/0.06	-0.32	(-0.88, 0.24)	0.26/0.24	-0.10	(-0.26, 0.07)	0.24/0.31
<u>Density (spindles/ min)</u>									
Central, slow	0.00	(0.00, 0.01)	0.35/0.04	-0.06	(-0.10, -0.02)	>0.001/0.01 <sup>†</sup>	0.01	(-0.01, 0.02)	0.32/0.14
Central, fast	0.00	(-0.01, 0.01)	0.86/0.91	-0.05	(-0.11, 0.02)	0.14/0.07	0.01	(-0.01, 0.03)	0.58/0.61
Frontal, slow	0.00	(-0.01, 0.01)	0.97/0.59	-0.08	(-0.14, -0.02)	0.01/0.01 <sup>†</sup>	0.00	(-0.02, 0.01)	0.64/0.73
Frontal, fast	0.00	(-0.01, 0.01)	0.83/0.98	-0.04	(-0.09, 0.02)	0.19/0.16	0.01	(-0.01, 0.02)	0.58/0.53
<u>Frequency</u>									
Central, slow	0.00	(-0.01, 0.01)	0.76/0.16	-0.10	(-0.17, -0.03)	0.01/0.01 <sup>†</sup>	-0.01	(-0.03, 0.02)	0.67/0.85
Central, fast	0.00	(-0.01, 0.01)	0.82/0.64	0.02	(-0.02, 0.05)	0.35/0.48	0.00	(-0.01, 0.01)	0.82/0.67
Frontal, slow	0.00	(-0.01, 0.01)	0.84/0.67	-0.06	(-0.11, -0.02)	0.01/>0.001 <sup>†</sup>	0.00	(-0.02, 0.01)	0.55/0.46
Frontal, fast	0.00	(0.00, 0.00)	0.80/0.94	0.03	(0.01, 0.05)	0.01/>0.001 <sup>†</sup>	0.00	(0.00, 0.01)	0.33/0.35

\*p<sup>1</sup> represents significance for Model 1; p<sup>2</sup> represents significance for Model 2.

<sup>†</sup> Significant association that survives controlling for multiple testing.

**Table 4** –Associations between boys’ false memory task performance and sleep spindles adjusted for age (Model 1); p-values presented for both Model 1 and Model 2 (controlled for age, pubertal development and estimated IQ).

	Correctly recalled words			Critical lures			Intrusions		
	B	(95% CI)	*p1/p2	B	(95% CI)	*p1/p2	B	(95% CI)	*p1/p2
<u>Amplitude (μV)</u>									
Central, slow	0.01	(-0.19, 0.22)	0.89/0.94	0.34	(-0.93, 1.61)	0.60/0.99	0.01	(-0.41, 0.42)	0.98/0.71
Central, fast	0.05	(-0.13, 0.23)	0.59/0.86	-0.16	(-1.30, 0.98)	0.78/0.64	-0.12	(-0.49, 0.25)	0.52/0.72
Frontal, slow	0.09	(-0.09, 0.28)	0.32/0.30	-0.01	(-1.14, 1.12)	0.99/0.82	-0.07	(-0.46, 0.33)	0.74/0.74
Frontal, fast	0.03	(-0.10, 0.16)	0.64/0.57	-0.25	(-1.04, 0.55)	0.54/0.61	-0.02	(-0.30, 0.26)	0.88/0.81
<u>Density (spindles/ min)</u>									
Central, slow	-0.01	(-0.02, 0.01)	0.29/0.53	0.00	(-0.07, 0.07)	0.95/0.98	0.01	(-0.02, 0.03)	0.61/0.56
Central, fast	0.00	(-0.01, 0.01)	0.58/0.44	0.02	(-0.05, 0.09)	0.57/0.43	0.01	(-0.02, 0.03)	0.56/0.26
Frontal, slow	0.00	(-0.02, 0.01)	0.81/0.95	0.00	(-0.10, 0.10)	0.99/0.94	0.00	(-0.03, 0.03)	0.98/0.81
Frontal, fast	0.00	(-0.01, 0.01)	0.95/0.61	-0.06	(-0.14, 0.02)	0.13/0.18	-0.01	(-0.03, 0.02)	0.70/0.76
<u>Frequency</u>									
Central, slow	0.01	(-0.01, 0.02)	0.42/0.82	0.01	(-0.08, 0.10)	0.85/0.91	0.01	(-0.02, 0.04)	0.66/0.67
Central, fast	0.00	(-0.01, 0.00)	0.47/0.64	0.00	(-0.04, 0.04)	0.95/0.82	0.00	(-0.01, 0.01)	0.80/0.81
Frontal, slow	0.01	(0.00, 0.03)	0.08/0.20	0.03	(-0.05, 0.11)	0.48/0.37	0.01	(-0.02, 0.04)	0.36/0.10
Frontal, fast	-0.01	(-0.02, 0.00)	0.12/0.28	-0.03	(-0.08, 0.03)	0.35/0.32	0.00	(-0.02, 0.02)	0.78/0.53

\*p<sup>1</sup> represents significance for Model 1; p<sup>2</sup> represents significance for Model 2.



**Table 1** – Characteristics of the participants.

	Mean (SD) or N (%)		P
	Girls N=116 (59)	Boys N=80 (41)	
Birth weight, g	3532 (398)	3583 (497)	0.44
Highest parental education			0.997
Secondary or less	11 (10)	8 (10)	
Vocational	23 (21)	16 (21)	
University degree	77 (69)	54 (69)	
Age	16.90 (0.1)	16.90 (0.1)	0.97
BMI	22.5 (3.0)	21.7 (3.5)	0.11
Pubertal development <sup>1</sup>	3.45 (0.3)	3.00 (0.4)	<0.001
IQ, age-residualized estimate <sup>2</sup>	0.13 (0.7)	-0.17 (0.7)	0.003
Sleep variables			
Total sleep time (h:min)	7:43 (1:16)	7:23 (1:12)	0.08
Sleep efficiency (%)	92.84 (7.9)	92.00 (7.8)	0.48
Stage 1 sleep (%)	9.42 (4.1)	11.01 (4.3)	0.01
Stage 2 sleep (%)	39.07 (6.6)	36.90 (6.8)	0.03
Slow-wave sleep (SWS) (%)	24.65 (5.7)	25.75 (6.3)	0.22
Rapid eye movement (REM) (%)	19.69 (5.0)	18.34 (5.6)	0.09
Spindle amplitude (μV)			
Central, slow	26.10 (5.4)	25.49 (5.1)	0.48
Central, fast	23.19 (5.7)	18.58 (4.7)	<0.001
Frontal, slow	23.98 (5.6)	23.78 (4.9)	0.80
Frontal, fast	15.47 (3.9)	14.43 (3.4)	0.06
Spindle density (spindles /minute)			
Central, slow	0.48 (0.2)	0.51 (0.3)	0.52
Central, fast	0.79 (0.4)	0.59 (0.3)	<0.001
Frontal, slow	0.97 (0.4)	0.99 (0.4)	0.74
Frontal, fast	0.59 (0.4)	0.50 (0.3)	0.10
Spindle frequency			
Central, slow	11.89 (0.4)	12.08 (0.4)	0.01
Central, fast	13.66 (0.2)	13.55 (0.2)	<0.001
Frontal, slow	11.66 (0.3)	11.58 (0.4)	0.10
Frontal, fast	13.62 (0.2)	13.71 (0.2)	0.01
DRM memory task			
Correctly recalled words	16.1 (9.9)	10.4 (7.3)	≤0.001
Critical lures	1.9 (1.4)	1.5 (1.0)	≤0.01
Intrusions	6.1 (4.8)	4.4 (3.5)	≤0.01
False memory ratio <sup>3</sup>	0.14 (0.11)	0.19 (0.19)	0.04

<sup>1</sup>Pubertal development estimated using the Pubertal Development Scale (PDS).<sup>2</sup>An age-residualized Intelligence Quotient (IQ) estimate was calculated from Wechsler Adult Intelligence Scale III.<sup>3</sup>False memory ratio was calculated by dividing the number of critical lures by total number of correctly recalled studied words.



**Table 2** – Associations between DRM test performance and sleep stages (Model 1: controlled for age; Model 2: controlled for age, pubertal development and IQ).

	Correctly recalled words				Critical lures				Intrusions				
	B	(95 % CI)		*p <sup>1</sup> /p <sup>2</sup>	B	(95 % CI)		*p <sup>1</sup> /p <sup>2</sup>	B	(95 % CI)		*p <sup>1</sup> /p <sup>2</sup>	
<i>Girls,</i>													
<i>Model 1</i>													
Sleep duration	1.02	-0.44	2.48	0.17/0.12	5.14	-5.22	15.50	0.33/0.44	3.54	0.43	6.66	0.03/0.001	
N1 %	0.04	-0.03	0.12	0.26/0.08	0.15	-0.40	0.70	0.59/0.59	0.17	0.00	0.33	0.05/0.07	
N2 %	0.02	-0.11	0.15	0.72/0.92	0.29	-0.62	1.19	0.53/0.64	-0.04	-0.32	0.24	0.76/0.98	
N3 %	-0.08	-0.19	0.04	0.18/0.08	-0.49	-1.28	0.29	0.21/0.34	-0.11	-0.35	0.13	0.37/0.37	
REM %	0.04	-0.05	0.14	0.39/0.13	0.17	-0.51	0.85	0.62/0.41	0.04	-0.16	0.25	0.68/0.29	
<i>Boys,</i>													
<i>Model 1</i>													
Sleep duration	-0.79	-3.54	1.96	0.57/0.45	-1.87	-18.56	14.82	0.82/0.57	1.45	-4.29	7.19	0.62/0.71	
N1 %	0.08	-0.08	0.25	0.32/0.22	-0.22	-1.22	0.77	0.66/0.97	0.18	-0.16	0.52	0.30/0.15	

N2 %	-0.15	-0.41	0.11	0.24/0.14	-0.14	-1.73	1.44	0.86/0.61	-0.42	-0.95	0.12	0.13/0.14
N3 %	-0.04	-0.28	0.20	0.75/0.46	-0.23	-1.67	1.21	0.75/0.22	0.06	-0.44	0.55	0.82/0.59
REM %	0.03	-0.18	0.25	0.76/0.48	0.63	-0.67	1.93	0.34/0.48	0.45	0.01	0.88	0.05/0.14

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\*p1 represents significance for Model 1; p2 represents significance for Model 2.